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EXAMINER	
KIM, YOUNG J	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,301	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on February 8, 2006.

Preliminary Remark

Claim 4 is canceled. Claims 6-8 are newly submitted.

Claims 1-3 and 5-8 are under prosecution therefore.

Claim Rejections - 35 USC § 112 – Maintained

The **scope** of rejection of claims 1-3 and 5-8 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method involving the amplification which employs 40 ng of DNA per 100 sites, does not reasonably provide enablement for a method of amplification which employs lesser than 40 ng of DNA per 100 sites, made in the Office Action mailed on August 9, 20055 is withdrawn in view of the careful reconsideration of the application and the arguments presented in the Amendment received on February 8, 2006.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The new matter rejection of claims 1-3 and 5-8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on August 9, 20055 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on February 8, 2006 have been fully considered but they are not found persuasive for the following reasons.

Applicants contend that the legal test for adequacy of written description is whether on of ordinary skill in the art who reads the specification would understand the inventors to be in

"possession" of the invention as claimed (page 3, Response). Applicants state that the specification expressly states this detection level at 40 ng of input DNA in a working example, and thus based on this example, Applicants appear to contend that the description of the claims was fully provided and that Examiner failed to demonstrate sufficiently any reason to doubt that the 98% or greater detection efficiency of the described method should be less when an amount of input DNA other than 40 ng input DNA is used (page 3, 4th paragraph, Response).

As MPEP 2163(I) states, "[t]he issue raised in the cases is most often phrased as whether the original application provides "adequate support" for the claims at issue or whether the material added to the specification incorporates "new matter" in violation of 35 U.S.C. 132."

MPEP 2163.07 gives some guidance in when an amendment does not introduce new matter:

(I) Rephrasing: mere rephrasing of a passage does not constitute new matter;

(II) Obvious errors: an amendment to correct an obvious error does not constitute new matter;

(III) Inherent Function, Theory, or Advantage: *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill";

It is clear that the claim amendment drawn to a method which employs a range of amount of genomic DNA (the range of which being 10-40 ng) per 100 sites, wherein the method results in at least 98% of single nucleotide polymorphisms are detected does not qualify under "rephrasing," "obvious errors," or "inherent function."

One of skill in the art, in determining whether applicants had contemplated the invention as embraced by the claim amendment, must determine the full-breadth the claim now embraces.

The full breadth of the claims embraced by the claims are drawn to a method which simultaneously amplifies as little as two SNP sites to a plurality of SNP sites (100, 10,000, 100,000 sites), wherein the amount of genomic DNA employed for amplification is 10-40 ng per 100 sites. The amplified products are then typed by an assay, which results in 98% of single nucleotide polymorphisms.

Of course, for at least 98% of the SNPs to be detected, at least 98% of the SNPs must be amplified, simultaneously.

Applicants rely on a single description wherein 40 ng of starting DNA (page 15, second paragraph) is employed for simultaneously amplifying 100 target sites (page 15, 3rd paragraph), followed by the Invader assay typing for single nucleotide polymorphisms in the resulting amplicons (page 18, 1st paragraph), which resulted the detection of fluorescence in 98% of SNPs (page 19, 1st paragraph).

One of skill in the art would clearly recognize that at some point, the ability to simultaneously amplify a plurality of SNP sites, the plurality being much greater than 100 sites (as the claims do not have an upper limit) would fail, clearly, with the ability to amplify at least 98% of the SNP sites.

Thus, one of skill in the art would not recognize that Applicants were in possession of the full-breadth of the instantly claimed invention based on a single example of amplifying 100 sites using 40 ng of genomic DNA, wherein at least 98 of the sites were amplified and detected.

It should be noted that *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973), the court also expressed that when determining new

matter, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

As one of skill in the art would be not able to find any support that the full breadth of the claimed method would result in amplification of at least 98% of all SNP sites targeted, the support for the newly introduced limitation would appear to be based on an assumption, to which the court held insufficient.

The rejection is maintained therefore.

Claim Rejections - 35 USC § 102

The rejection of claims 1 and 5 under 35 U.S.C. 102(b) as being anticipated by Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343), made in the Office Action mailed on August 9, 2005 is withdrawn in view of the arguments presented in the Amendment received on February 8, 2006. Applicants are correct in their argument that Mein et al. do not explicitly disclose that the amplification was multiplexed (i.e., simultaneously amplified).

Claim Rejections - 35 USC § 103

The rejection of claims 3 and 7 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082), made in the Office Action mailed on August 9, 2005 is withdrawn in view of the arguments presented in the Amendment received on February 8, 2006.

Specifically, the record should be clear that this rejection is being withdrawn based on the reasoning applied in the combination of the references based on the perceived teachings of the references.

Note that claims 3 and 7 are rejected under the same statute in the below rejection based on a different reasoning from that which was employed in the previous Office Action mailed on August 9, 2005.

The rejection of claims 2 and 6 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Brooks (US 2001/0046670 A1, issued November 29, 2001, priority October 7, 1999), made in the Office Action mailed on August 9, 2005 is withdrawn in view of the arguments presented in the Amendment received on February 8, 2006. Applicants are correct in their argument that Mein et al. do not explicitly disclose a multiplex amplification involving plurality of primers (i.e., simultaneously amplified) and as Brooks does not cure this deficiency, the rejection must fall.

The rejection of claim 8 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082) and Brooks (US 2001/0046670 A1, issued November 29, 2001, priority October 7, 1999) made in the Office Action mailed on August 9, 2005 is withdrawn in view of the arguments presented in the Amendment received on February 8, 2006.

Specifically, the record should be clear that this rejection is being withdrawn based on the reasoning applied in the combination of the references based on the perceived teachings of the references (Mein et al. reference in particular).

Note that claim 8 is rejected under the same statute in the below rejection based on a different reasoning from that which was employed in the previous Office Action mailed on August 9, 2005.

Rejection, New Grounds

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082).

Preliminarily, the full-breadth of the claims are construed as follows.

The limitation imposed by the phrase, "genomic DNA whose amount is 10-40 ng per 100 sites," embodies a range of 0.1 ng to 0.4 ng per a single SNP site. Thus, the method requires at least 0.2 ng of genomic DNA in claims 1 and 3 which recite the step of simultaneously amplifying "at least two sites," and at least 0.1 ng of genomic DNA in claims 5-8 which recite the step of simultaneously amplifying one or more sites."

Additionally, claims 7 and 8 does not require that the 50 pairs of more primer be primer pairs which amplifies different SNP sites. Thus, employing at least 50 pairs of the primer pairs which amplify a single SNP site (i.e., having the same sequences) would necessary meet this limitation.

While Applicants' arguments are moot in view of this new ground of rejection, to the extent applicable, the arguments will be addressed in the, "Response to Arguments" section.

Mein et al. disclose a method of coupling multiplex amplification of polymorphic loci from a genomic DNA, followed by detecting the single nucleotide polymorphisms by Invader® assay method (Abstract, page 331, 2nd column).

Mein et al. disclose that 36 SNPs sites were amplified (page 331, 2nd column), employing 10 ng of starting DNA. Mein et al. are silent as to how many SNP sites were simultaneously amplified using the 10 ng of starting DNA.

Hence, Mein et al. do not employ 50 or more primer pairs in their method nor genomic DNA whose amount is 10-40 ng per 100 sites.

Wang et al. disclose a method of detecting SNPs by first simultaneoutly amplifying (or multiplexing) a plurality of primer pairs, including 558 loci, necessarily including more than 50 primer sets, considering that a singe primer set amplifies a single loci (page 1080, 3rd column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Mein et al. with the teachings Wang et al. to arrived at the claimed invention for the following reasons.

The motivation to multiplex more target sites in amplification, that is, simultaneously amplifying multiple target sites, is a well-established desire in the art. As Wang et al. put it:

> "We next sought to **decrease substantially the sample preparation required to generate large numbers of SNPs, as required to perform a genome scan. We developed a protocol based on multiplex PCR in which primer pairs from many different loci are combined in a single reaction**." (page 1080, 3rd paragraph, 1st paragraph)

Wang et al. employ 100 ng of DNA for simultaneously amplifying a plurality of loci, including 24 sets of approximately 23 loci, 12 sets of approximately 46 loci, 6 sets of approximately 92 loci (page 1080, 3rd paragraph, 1st paragraph), and a single set of 558 loci.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. with the teachings of Wang et al. to arrive at simultaneously amplification involving at least 50 pairs of primers or more.

Wang et al. disclose that 12 sets of 46 loci; (46 loci being amplified simultaneously); 6 sets of 92 loci; a single set of 558 loci were amplified simultaneously (page 1080, 3rd column).

While the artisans disclose that different multiplex amplification reactions gave different percentage of loci being successfully amplified, Wang et al. explicitly discusses that it may be possible to salvage the unsuccessful assays by grouping them into additional multiplex sets or by *redesigning* the assays.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. and the teachings of Wang et al. to achieve multiplex amplification involving a plurality of primers for the advantage of decreasing sample preparation (as expressed by Wang et al.), wherein the artisan would have had a reasonable expectation of success at such combination as Wang et al. clearly envisions that by redesigning, multiplexing even up to 558 loci would be achievable, through optimization.

Regarding optimization, the MPEP 2144.05(II)(A) clear that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995). Analogously, optimizing parameters for multiplexing

multiple target sites in an amplification reaction would be considered routine, as provided for by Wang et al.

In addition, based on the fact that a single multiplex amplification involving 100 ng of DNA for amplifying 558 loci resulted in a 50% success, one of ordinary skill in the art would have had a reasonable expectation of success at employing half the number of the loci (approximately 279 loci), with the 100 ng of starting DNA (which would result in 0.36 ng per target site) with close to a 100% success.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants contend that the position taken in the previous Office Action is inconsistent since the enablement rejection was based on the unpredictability of simultaneously amplifying a plurality of target sites employing low amounts of starting DNA, while taking the position of obviousness as being routine optimization.

The enablement rejection has been withdrawn in careful reconsideration, so this argument is moot.

In addition, Applicants contend that the teachings of "Wang et al. actually teaches away from the present invention." (page 4, bottom paragraph, Response).

This argument is not found persuasive because Wang et al. not only provide motivation to multiplex a plurality of target sites in a single reaction vessel, but also optimize the condition to achieve higher success rate.

> "We next sought to decrease substantially the sample preparation required to genotype large numbers of SNPs, as required to perform a genome scan."
> "It may be possible to salvage the unsuccessful assays by grouping them into additional multiplex sets or by redesigning the assays." (page 1080, 3rd column).

While Wang et al. does not explore all conditions so as to optimize their multiplex amplification reaction, it is maintained that such would involve routine optimization of an ordinarily skilled artisan.

Finally, Applicants assert that the rejection would be improper since the combination of the references, "at best, describe a multiple PCR that produces a failure rate of 50% when as little as 10-40 ng of gnomic DNA are utilized."

This argument is not found persuasive based on the fact that a single multiplex amplification involving 100 ng of DNA for amplifying 558 loci resulted in a 50% success, one of ordinary skill in the art would have had a reasonable expectation of success at employing half the number of the loci (approximately 279 loci), with the 100 ng of starting DNA (which would result in 0.36 ng per target site) with close to a 100% success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 2, 6, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082) as applied to claims 1, 3, 5, and 7 above, and further in view of Brooks (US 2001/0046670 A1, issued November 29, 2001, priority October 7, 1999).

The teachings of Mein et al. and Wang et al. have already been discussed above.

Neither Mein et al. nor Wang et al. employ "hot start" amplification (claims 2, 6, and 8)

Brook discloses a multiplex amplification [0076] reaction which involves hot start amplification [0066].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mein et al., and Wang et al. with the advantage offered by Brooks to arrive at the invention as claimed for the following reasons.

Brook clearly discusses the advantage of employing "hot start" PCR method:

"...other 'Hot Start' type PCR conditions are used to limit primer dimer artifacts as much as possible." [0066].

As one of ordinary skill in the art in the art of amplification would recognize that primer dimer artifacts are to be minimized in amplification procedures, it would have been obvious to implement this teachings into the teachings of Mein et al., and Wang et al. to arrive at the claimed invention with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants do not present any new arguments than those which were fully addressed above.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
4/5/2006

YOUNG J. KIM
PATENT EXAMINER

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